European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 1998; 2(3-4): 141-145

Prospective study of preincisional single-dose ceftriaxone in reducing postoperative wound infection in high risk of infection patients

I. PETRAKIS, N. VRACHASSOTAKIS, A. TSATSAKIS, G. CHALKIADAKIS

Departments of General Surgery and Toxicology, University Hospital of Herakleion, University of Crete – (Greece)

Abstract. – ***Background-Aims:*** **The risk of wound contamination in high risk of infection patients after abdominal operations is well recognised. Preincisional intraparietal injection of antibiotics is used for the prophylaxis of postoperative surgical infections. Whether topically injected antibiotics remain primarily in the surgical wound or are systematically absorbed is uncertain, however.**

Patients and Methods: **The pharmacokinetic of preincisional injection of 2 g Ceftriaxone were studied in 50 high risk of infection patients (diabetic, oncologic, immunocompromised and obese) who have undergone abdominal surgery, with determination of serum, wound tissue, and wound fluid antibiotic concentrations.**

Results: **Preincisional injection of Ceftriaxone resulted in high antibiotic concentrations in the wound fluid. The highest plasma concentrations were achieved at 1½ hours (118.40 SD 38.43µg/ml). Plasma concentrations exceeded the minimal inhibitory concentrations of most aerobic gram positive and gram negative organisms with the exception of Pseudomonas aeruginosa, Acinobacter species, and Streptococcus faecalis for 24 hours (10.10 SD 4.00 µg/ml). No longer or general complications were arose in any of the patients.**

Conclusion: **Our results suggest that preincisional administration of ceftriaxone for prophylaxis of the wound sepsis in high risk of infection patients is very effective.**

Key-Words:

Ceftriaxone, Preincisional Intraparietal, Infection, Surgery.

Introduction

It is well recognised that the most important factor in the pathogenesis of wound sepsis is the presence of bacteria in the incision at the time of closure[1-3]. Recent studies on the prevention of postoperative would infections advocate the use of prophylactic antibiotics, especially in cases of oncologic, immunocompromised, obese and diabetic patients where the risk of contamination is high, while other studies reveal a high index of surgical wound infection after surgery in such patients[4-9]. An appropriate antibiotic administrated intravenously in a single dose prior to surgery (preoperative prophylaxis) ensures high blood levels of the antibiotic at the time of wound closure and reduces wound infection, as well as other septic complications.

The concept of "preincisional - intraincisional" injection of antibiotics was introduced by Taylor et al[6] in 1982. This technique achieves high local concentrations of antibiotic combined with adequate serum levels[10].

However, the purpose of this study was threefold: to determine the actual levels of antibiotic in the high risk of infection patients (diabetic, oncologic, immunocompromised and obese) serum, surgical wound edges, and fluid from the surgical wound during the operation and 24 hours postoperatively; to compare the found values with the already reported pharmacokinetic data of intravenous (IV) and intramuscular (IM) injections of ceftriaxone in healthy volunteers[11-13], and to evaluate the effectiveness of the intraparietal administration, in a prospective controlled study.

Ceftriaxone an antibiotic with long half life, was chosen because of its known effectiveness against a wide rage of wound pathogens, including obligate anaerobes, at concentrations likely to be present locally. The simultaneous

measurement of serum, wound tissue edges, and wound fluid antibiotic concentration of ceftriaxone in the high risk of infection patients undergoing abdominal surgery has not been reported, to our knowledge.

Patients and Methods

Fifty patients with high risk of wound infection (diabetic oncologic, immunocompromised and obese) undergoing abdominal surgery were studied. The operations were cholecystectomy (7 patients), vagotomy and pyloroplasty (4 patients), vertical gastroplasty (3 patients) small bowel occlusion (4 patients), oesophageal cancer (2 patients), colorectal cancer (9 patients), appendectomy (3 patients), gastric cancer (4 patients), gastrectomy (2 patient), pancreatic (4 patients), hepatic and biliary tract neoplasias (5 patients) ovarian neoplasias (2 patient) and hysterectomy (1 patient).

The patients' ages ranged from 34 to 77 years. Each patient received a local injection of ceftriaxone (2 g in 20 ml normal saline) 10 minutes before the start of the operation. Injection was carried out using a 22-Fr spinal cord needle subcutaneously (and often, in thin patients, intramuscularly) along the line of the proposed abdominal incision, with a careful attempt being made to perform uniform infiltration along the incision. The wounds were an average of 20 cm long; thus approximately 1 ml of antibiotic solution was injected along each centimetre. Tissue samples were taken from three areas of the wound at the end of the operation. In all patients, fine perforated polyethylene tubes were placed in the subcutaneous plane of the wounds and connected to evaluated bottles (Redovac, Sterimed, Saarbrucken, Germany) for the collection of the wound fluid during a period of 24 hours after the operation.

Blood samples were taken at 30 minutes and at 1, 1 1/2, 2, 3, 4, 5, 6, 12 and 24 hours. The blood was immediately centrifuged, and the serum separated and stored at -20°C until high-pressure liquid chromatography (HPLC) analysis was performed.

Laboratory Methods

Plasma samples and wound fluid were prepared (using the method described earlier) with protein precipitation with ethanol. Tissues were homogenised with water, the homogenate was centrifuged, the supernatant was filtered through a Minisart filter with 0.2 mm pore size (Sartorious GmH, Goittingen, Germany), and the filtrate was injected to the HPLC system[14]. For the quantification of the ceftriaxone in tissues, water ceftriaxone standards were used.

The reversed phase HPLC analysis was performed by using an APEX ODS II SU column (Jones Chromatography Ltd., Hengoed, United Kingdom) with ultraviolet detection at 273 mm. The mobile phase was a system solution containing acetonitrile (39.4%), water (55.2%), hexadecyltrimethylammonium bromide (0.4%), and Titrisol buffer (E. Merc, Darmstadt, Germany) pH 7 (5%). The internal standard used was phthalic acid. In the above mentioned conditions, the ceftriaxone and phthalic acid signal appeared in the chromatogram with a retention time of 5.11 and 7.12, respectively.

Statistical Analysis

The data are reported as mean values and standard deviations (SD), of ceftriaxone concentration in fluids and tissues and were performed using a statistical software package (Statgraphics, STSC Inc, Rockville, Maryland).

Results

There were no complications following injection nor did any would infection occur. The mean plasma concentrations are shown in Table I and the Figure. The concentrations of ceftriaxone in fluid from the wound and the tissue from the wound are shown in Table II. The results demonstrate that preincisional injection of ceftriaxone gives desirable serum levels with peak plasma concentration of 98.30 SD 14.10 μg/ml found after 1½ SD 1/2 hours and a mean plasma concentration of 10.10 SD 4.00 μg/ml after 24 hours.

Tissue concentrations measured at the end of the operation were higher than the corresponding plasma concentrations. These high tissue levels of ceftriaxone were maintained for the length of the operation and were constantly higher than the highest plasma concentration ceftriaxone.

Table I. Plasma concentration of Ceftriaxone during operation and postoperatively (during a 24-hour period) in 50 high risk of infection patients (diabetic, oncologic, immunocompromised and obese) undergoing surgery.

Time (hrs) after 2 g preincisional injection of ceftriaxone solution*	*Plasma concentration (μg/ml)*
0	0
0.5	98.90 ± 17.53
1	110.40 ± 34.21
1.5	118.40 ± 38.43
2	104.30 ± 30.70
3	89.93 ± 28.42
4	80.30 ± 22.88
5	73.27 ± 28.78
6	62.07 ± 21.25
12	36.15 ± 14.70
24	18.42 ± 6.10

Data report as mean ± standard deviation. *Sampling time deviation: ± ½ hour.

Discussion

Wound infection remains an important postoperative complication with significant clinical and economic consequence[15], mostly in high-risk patients, as are the diabetics the obese, the oncologic (and the immunocompromised)[4-9,16,17]. Moylan[18] estimated its occurrences in the United States in 7% to 8% of all operations, while Lumley et al after intravenously administration of the same antibiotic reports an incidence of 7.9% of wound contamination after colorectal surgery[19]. After surgery of the gastrointestinal tract, wound infections are nearly always caused by intestinal organisms being released and disseminated into the incision during the operation[10]. From the study of 1,000 general surgical operations, Davidson et al[3], clearly showed that the most important factor in the pathogenesis of wound sepsis was the pretence of bacteria at the time of would closure. Delgado-Rodriguez et al[20] found that obese or immunocompromised patients undergoing abdominal surgery showed a statistically significant association with postoperative pneumonia risk after wound infection.

The goal of surgical prophylaxis is to ensure that a satisfactory tissue concentration of a drug with a reasonable spectrum activity against expected organisms is achieved and maintained during the period of potential

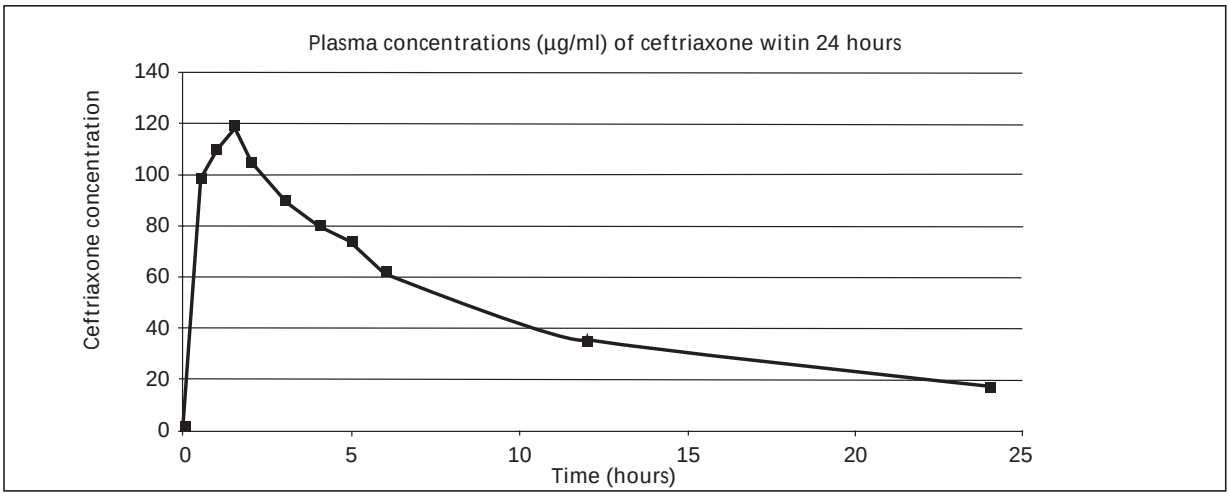

Figure 1. Plasma concentrations (μg/ml) of ceftriaxone within 24 hours. Values were fitted on a curve obtained from a biexponential pharmacokinetic formula based on an open one-compartment model. (■ Actual —— Fitted).

Table II. Concentration of Ceftriaxone in surgical wound tissue measured at the end of each operation* and in the fluid from the surgical wound.

	Concentration		
Sample	**A**	**B**	**C**
Wound Tissue (µg/ml), (range)	1.581 ± 488, (890-2,020)	950 ± 380, (370-1.440)	330 ± 280, (110-810)
Fluid from the Wound°	1.119 ± 405, (470-1540)	720 ± 320, (210-1110)	250 ± 110, (90-320)

Data report as mean ± standard deviation.
*Operation time period range: A = from 40 to 70 min; B = from 70 to 120 min; C = from 120 to 180 min.
°The fluid was collected and measured 24 hours postoperatively.

bacterial contamination of the wound, so that organisms introduced into the wound during the operation would be destroyed immediately. Failure to maintain adequate serum and tissue levels throughout the surgical procedure increases the likelihood of the infection[21]. Polk and Lopez-Mayor[22], have emphasized that wounds levels, not blood or serum levels, appear to determine the efficacy of agents for prophylaxis of operative wound infection. These very high tissue levels could only achieved by a preoperative intraincisional injection.

Prophylactic antibiotics are generally administered systemically prior to operation[15]. Under experimental conditions, antibiotics have been shown to be effective only if given within 4 hours of inoculating bacteria into a wound[10]. The concentration of an appropriate antibiotic in the wound itself, rather than in the serum, is the critical factor in determining the efficacy of agents used for the prophylaxis of surgical wound infection[23].

We have shown that high concentrations of antibiotic are present in the wound throughout the operation if a preincisional injection of an antibiotic is given and are likely to kill any sensitive bacteria that contaminate the wound (Table II). The mean plasma concentrations of ceftriaxone (Table I) are comparable with results of pervious studies when the antibiotic was given intravenously or intramuscularly[11-13]. But the fact that with this technique we have achieved good plasma concentrations of ceftriaxone means the antibiotic returns to the wound by the systemic route as well, and we consider that we have a higher concentration of the drug in the surgical wound compared to both, intravenously and intramuscular administration.

At 6 to 12 hours, concentrations of free drug are above the minimum inhibitory concentrations (Table I) for staphylococci and streptococci (excluding Pseudomonas aeruginosa, Acinobacter species, and Streptococcus faecalis) and for organisms such as Escherichia coli and Klebsiella, Proteus, and Haemophilus species[11]. Indeed, the ceftriaxone concentrations in serum present at 24 hours (10.10 SD 4.00 µg/ml) exceed the minimal bactericidal concentrations of most streptococcal species, Haemophilus influenzae, and many of the Enterobacteriaceae, including ßlactamase-producing strains[11].

In conclusion, the results of the present study suggest that preincisional injection of ceftriaxone in all the high infection risk patients, as are the diabetics, could protect them against septic complications occurring in other sites. Preincisional injection of ceftriaxone should be beneficial in two ways; very high wound levels will prevent wound sepsis, and good serum levels will minimise systemic complications for 24 hours.

References

1) *Chalkiadakis EG, Gonianakis C, Tsatsakis A, Tsakalof A, Michalodimitrakis M*. Preincisional single-dose ceftriaxone for the prophylaxis of surgical wound infection. Am J Surg 1995; 170: 353-355.
2) *Dixon JM, Armstrong CP, Duffy SW, Chetty U, Davies GC*. A randomised prospective trial comparing the value of intravenous and preincisional cefamandole in reducing postoperative sepsis after operations upon the gastrointestinal tract. Surg Gyn Obstet 1984; 158: 303-307.
3) *Davidson AIG, Clark G, Smith G*. Postoperative wound infection: a computer analysis. Br J Surg 1971; 58: 333-337.

4) THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329: 977-986.

5) *POLLOCK AV.* Surgical wound sepsis. Lancet 1979; 1: 1283-1286.

6) *TAYLOR TV, WALKER WS, MASON RC, RICHMOND J, LEE D.* Preoperative intraparietal (intraincisional) cefoxitin in abdominal surgery. Br J Surg 1982; 69: 459-460.

7) *VELASCO E, THULER LC, MARTINS CA, DIAS LM, GONCALVES VM*. Risk index for prediction of surgical site infection after oncology operations. Am J Infect Control 1998; 26: 217-223.

8) *RANCHERE JY, GORDIANI B, BACHMANN P*. Postoperative infections in immunocompromised patients after oncological surgery. Support Care Cancer 1995; 3: 409-413.

9) *BARBER GR, MIRANSKY J, BROWN AE, COIT DG, LEWIS FM, THALER HT, KIEHN TE, ARMSTRONG D*. Direct observations of surgical wound infection at a comprehensive cancer center. Arch Surg 1995; 130: 1042-1047.

10) *ARMSTRONG CP, TAYLOR TV, REEVES DS.* Preincisional intraparietal injection of cefamandole: a new approach to wound infection prophylaxis. Br J Surg 1982; 69: 308-309.

11) *SCULLY BE, FU KP, NEU HC*. Pharmacokinetics of ceftriaxone after intravenous infusion and intramuscular injection. Am J Med 1984; 77: 112-116.

12) *BRICAIRE F, CASTAING JL, POCIDALO JJ, VILDE JL*. Etude de la pharmacocinétique et de la tolérance de la ceftriaxone administré par voie sous-cutané. Path Biol Paris 1988; 36: 702-705.

13) *BORNER K, LODE H, HAMPEL B, PFEUFFER M, KOEPPE P*. Comparative pharmacokinetics of ceftriaxone after subcutaneous and intravenous administration. Chemotherapy 1985; 31: 237-245.

14) *TRAUTMAN K, HAEFELFINGER P*. Determination of the cefalosporin Ro 13-9904 in plasma, urine and bile by means of ion-pair reversed phase chromatography. J High Resol Chromatogr Chrom Commun 1981; 4: 54-59.

15) *FOSTER GE, BOURKE JB, BOLWELL J et al*. Clinical and economic consequences of wound sepsis after appendectomy and their modification by metronidazole or povidone-iodine. Lancet 1981; 1: 769-771.

16) *BROWNLEE M, CERAMI A, VLASSARA H*. Advanced glycosylation and products in tissue and the biochemical basis of complications. N Engl J Med 1988; 388: 1315-1321.

17) *WILLIAMSON JR, CHANG K, FRANGOS M et al*. Hyperglycemic pseudohypoxia and diabetic complications. Diabetes 1993; 42: 801-813.

18) *MOYLAN JA*. The proper use of local antimicrobial agents in wounds. World J Surg 1980; 4: 433-437.

19) *LUMLEY JW, SIU SK, PILLAY SP et al*. Single dose ceftriaxone as prophylaxis for sepsis in colorectal surgery. Aust N Z J Surg 1992; 62: 292-296.

20) *DELGADO-RODRIGUEZ M, MEDINA-CUADROS M, MARTINEZ-GALLEGO G, SILLERO-ARENAS M*. Usefulness of intrinsic surgical wound infection risk indices as predictors of postoperative pneumonia risk. J Hosp Infect 1997; 35: 269-276.

21) *SCHER KS, PEOPLES JB*. Combined use of topical and systemic antibiotics. Am J Surg 1991; 161: 422-425.

22) POLK HC, LOPEZ-MAYOR JFA. Postoperative wound infections: postoperative study of determinant factors and prevention. Surgery 1969; 19: 670-672.

23) *MATUSHEK KJ, ROSIN E*. Pharmacokinetics of cefazolin applied topically to the surgical wound. Arch Surg 1991; 126: 890-893.